chemical profile for defining fiber types. Type I fibers are characterized by relatively high mitochondrial oxidative enzyme activity in contrast to type II fibers, which rely more on glycogen as an energy substrate. Morphometric analysis of preferential change in fiber types permits recognition of diseases selective for specific fiber types. Such analysis is useful in determining congenital fiber-type disproportion (CFTD) or fiber-type grouping typical of reinnervation. Abnormal aggregations of mitochondria are typical of the "ragged red" neuromyopathies and other mitochondrial myopathies. Abnormal activity of the lysosome system identified by acid phosphatase deposition in fibers is characteristic of chloroquine myopathies and acid maltase deficiency (Pompe's disease). Histochemical semiquantitative estimation of enzyme activity may be of help in defining enzyme deficiencies such as myophosphorylase and phosphofructokinase deficiencies, both associated with abnormal ischemic forearm tests.

Electron microscopy is expensive and often unrewarding. Ultrastructural examination should be reserved for selected muscle specimens in which histochemical abnormalities have been identified. Abnormal reactions primarily affecting myofilaments with the formation of ring fibers and target fibers, abnormalities of the transverse Z band with the formation of nemaline inclusions (nemaline myopathy) and confirmation of abnormal mitochondria in the mitochondrial myopathies are typical examples. Unusual organelles including tubular aggregates, masses of myeloid bodies and fingerprint inclusion bodies add specificity to the classification of muscular disease.

Direct immunofluorescence has been applied to the evaluation of muscle disease. Vascular, fiber, perimysial and sarcolemma-basement membrane depositions of immunoglobulins have been identified in patients with connective tissue disorders. Often, to evaluate for the presence of selected neuromyopathies, biochemical analysis is required. For instance, a case of atypical central core disease was found to have a specific deficiency of fructose 1,6-diphosphatase. Another unusual case concerned a 60-year-old woman in excellent health in whom acute cramping and myoglobinuria suddenly developed after heavy exertion and who was found to lack myophosphorylase (McArdle's disease). Recently, electrophoretic techniques have disclosed some genetic heterogeneity of myophosphorylase deficiency in which some patients were found to lack the enzyme activity but retained the enzyme protein. Our case underwent sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis, which revealed the absence of the myophosphorylase band corresponding to that group lacking both enzyme and protein moieties. The evaluation of long-standing cramps with or without muscle weakness occasionally reveals increased intrafiber lipid. In such cases a biopsy specimen must be analyzed for carnitine and appropriate carnitine transferase activities.

In summary, the application of recent technologies provide a greater understanding of the evolution, natural history and pathogenesis of human neuromuscular disease. The minor discomfort of the technical procedure is greatly overshadowed by the wealth of diagnostic and prognostic information forthcoming from more refined analysis.

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Amniocentesis

THE NEED TO study fetuses at risk for Rh incompatibilty led to the development of widespread interest in the physiopathology of amniotic fluid and the living cells it contains. Amniocentesis is a safe, well-established procedure done yearly on thousands of pregnant women at risk for a variety of disorders.

The amniotic fluid is generated by the fetal kidneys and lungs and constantly recycled through fetal swallowing. Most amniotic cells are dead or degenerating but a small proportion can be cultured. These cultures contain a variety of slow-growing epithelial cells and fast-growing mesenchymal cells that share many morphologic and biochemical properties with cultured skin fibroblasts.

Amniotic fluid contains phospholipids whose changing composition reflects fetal maturity. This has been exploited for the assessment and prevention of hyaline membrane disease. The association of elevated α-fetoprotein with neural tube defects has led to their early detection. Mucopolysaccaride analysis may occasionally help in the rapid identification of fetuses affected by a mucopolysaccharide storage disorder. A variety of enzymes, including lysosomal hydrolases, can be analyzed but this has not led to practical diagnostic techniques. Most types of urine analysis can be carried out on the amniotic fluid, but this test is often neglected.

The study of freshly pelleted amniotic cells has limited applications but has allowed early diagnosis of selected storage disorders. Fabry's and Sandhoff's diseases and mucolipidosis IV can be detected by ultrastructural demonstration of characteristic inclusions that are not affected by cell degeneration.

Culture of amniotic cells is most commonly used for chromosome analysis and sex determination. Banding techniques have considerably increased the scope of identifiable chromosomal abnormalities. Sex determination has been used for families with crippling X-linked disorders not yet diagnosable in utero, such as Duchenne type muscular dystrophy or hemophilia. More than 30 types of lysosomal storage disorders can be diagnosed by enzyme determination on cultured amniotic cells. Using an elegant technique of DNA molecular hybridization, α-thalassemia can be diagnosed in amniotic cultures. This opens the way to the study of other mutations not expressed and therefore not directly detectable in these cells.

There is a crucial need for properly identifying fetuses at risk. This requires increasingly complex multidisciplinary cooperation. Too many genetic disorders are not recognized until two or more affected children are born in a family. Many probands hide behind such labels as cerebral palsy, multiple congenital abnormalities, autism or mental retardation. Only those families in which a specific chromosomal or biochemical abnormality has been found can benefit from prenatal diagnosis. Incomplete diagnosis, for example, "mucopolysaccharide storage disorder," not characterized by a comprehensive biochemical workup may prevent successful analysis of cultured amniotic cells in the time frame imposed by amniocentesis. Fluid may not be safely obtained before 12 to 14 weeks of pregnancy, and it takes at least three weeks but commonly six weeks to grow enough cells for a reliable analysis, whereas therapeutic abortion, if indicated, should be done no later than the 20th week. Ultramicrotechniques have been described that sometimes allow diagnosis on a single amniotic cell but large-scale practical application of this approach remains to be validated.

Screening groups with known risks, such as women 35 years old or older for trisomy 21, or Ashkenazi Jews for Tay-Sachs disease, has been highly successful. Most genetic disorders are undoubtedly rare but altogether they impose a disproportionate financial and psychological burden on families and, in the end, on the whole society.

Prenatal diagnosis has allowed a growing number of families at risk to have normal children by selected abortion of an affected fetus. Early treatment of abnormal fetuses would be much preferred but it is not conceivable in the near future.

The ethical issues involved have been hotly debated throughout the last decade. Genetic counseling is a relatively new discipline. No physician has a truly extensive experience in these problems, which vary widely with the specific disorders being monitored. A physician needs to guide and inform parents throughout the procedure. In most cases monitoring is of recessive disorders and therefore there is a 3:1 chance that the fetus will be normal or heterozygote. Some have advocated obtaining a primary commitment from parents that they will accept abortion if the fetus turns out to be affected. In practice some families who feel moral objections to a therapeutic abortion change their mind when confronted with the laboratory results. Meaningful counseling should not involve pressure or compulsion. Truly informed discussions whatever the ultimate parental decision are always mutually satisfying.

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Aspiration of Thyroid Nodules by Fine Needles

INVESTIGATORS at the University of California at Los Angeles and other American hospitals have recently obtained good results in diagnosing thyroid nodules by aspiration. The only surprise is that we have taken so long to apply this simple technique to the problem of thyroid nodules, when aspiration of the thyroid gland has been a standard diagnostic procedure in Sweden and other European countries for almost 30 years. A good specimen of cells and fluid can be obtained from a thyroid nodule by one or two aspirations